Year: 2017

Investigating motor skill learning processes with a robotic manipulandum

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DOI: https://doi.org/10.3791/54970

Originally published at:
Leemburg, Susan; Iijima, Maiko; Lambercy, Olivier; Nallet-Khosrofian, Lauriane; Gassert, Roger; Luft, Andreas (2017). Investigating motor skill learning processes with a robotic manipulandum. Journal of Visualized Experiments (Jove), (120):e54970.
DOI: https://doi.org/10.3791/54970

Title:

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Keywords
rodent, behavior, learning, motor skill, robot, forelimb, skilled reaching, movement kinematics

Short abstract

A paradigm is presented for training and analysis of an automated skilled reaching task in rats. Analysis of pulling attempts reveals distinct subprocesses of motor learning.

Long abstract

Skilled reaching tasks are commonly used in studies of motor skill learning and motor function under healthy and pathological conditions, but can be time-intensive and ambiguous to quantify beyond simple success rates. Here, we describe the training procedure for reach-and-pull tasks with ETH Pattus, a robotic platform for automated forelimb reaching training that records pulling and hand rotation movements in rats. Kinematic quantification of the performed pulling attempts reveals the presence of distinct temporal profiles of movement parameters such as pulling velocity, spatial variability of the pulling trajectory, deviation from midline, as well as pulling success. We show how minor adjustments in the training paradigm result in alterations in these parameters, revealing their relation to task difficulty, general motor function or skilled task execution. Combined with electrophysiological, pharmacological and optogenetic techniques, this paradigm can be used to explore the mechanisms underlying motor learning and memory formation, as well as loss and recovery of function (e.g. after stroke).

Introduction

Motor tasks are widely used to assess behavioral and neural changes related to motor learning or to alterations in motor function in neurological or pharmacological animal models. Fine motor function can be difficult to quantify in rodents, however. Tasks requiring manual dexterity, such as manipulation of cereal[1], pasta[2], or sunflower seeds[3] are sensitive and do not require extensive training of the animal. Their main drawback is that these tasks yield mostly qualitative results and can be difficult to score unambiguously.

Skilled reaching tasks, such as variations of the single pellet reaching task are more straightforward to quantify[4,5]. However, kinematic factors that underlie successful execution of these tasks can only be inferred to a limited extent and require labor-intensive frame-by-frame video analysis.

Robotic devices have gained popularity as means of quantifying aspects of forelimb function and motor skill. Several automated reaching tasks are available. The majority focus on a single aspect of a forelimb movement, such as pulling of a handle along a linear guide[6,7], simple distal limb movements[8], or pronation and supination of the paw[9]. While these devices show promise for the analysis of motor function in, they only reflect the complex motor actions executed during single pellet reaching to a limited extend.

Here, we demonstrate the use of a three-degree-of-freedom robotic device, ETH Pattus, developed for training and assessment of various motor tasks in rats[10,11]. It records planar and rotational movement of rat forelimb movements in reach, grasp and pulling tasks carried out in the horizontal plane. Rats interact with the robot via a 6 mm-diameter spherical handle that can be reached through a window in the testing cage (width: 15 cm, length: 40 cm, height: 45 cm) and moved in the horizontal plane (pushing and pulling movements) and rotated (pronation-supination movements). Thus, it enables the rat to carry out movements that approximate those executed during conventional single pellet reaching tasks. The window is 10 mm wide and located 50 mm above the cage floor. The handle is located 55 mm above the floor. A sliding door blocks access to the handle between reaching trials and opens when the robot reaches its start position and closes after a trial is completed. After a correctly executed movement rats receive a food reward on the opposite side of the testing cage.

The robot is controlled via Labview software and records output from 3 rotary encoders at 1000 Hz, resulting in information about the position of the handle in the horizontal plane, as well as its rotation angle (for details, see [11]). The conditions required for successful task execution are defined in the software prior to each training session (e.g. minimum required pulling distance and maximum deviation from midline in a reach-and-pull task). An initial standardized reference position of the handle is recorded with a fixed holder at the start of each training session. This reference is used for all trials within a session, assuring a constant start position of the handle for each trial. Constant positioning of the handle relative to the cage window is assured by alignment of marks on the cage and robot. (Figure 1)
Video recordings of the reaching movements are recorded using a small high speed camera (120 frames per second, 640x480 resolution). A small display in the camera's view shows the rat's identification number, training session, trial number and trial result (success or failed). These videos are used to verify recorded results and to assess the effects of reaching movements that precede the touching, pulling or rotation of the handle.

Here, we demonstrate the use of this robotic platform in variations of a reach-and-pull task. This task can be trained within a period of time that is comparable to other skilled reaching paradigms and yields reproducible results. We describe a typical training protocol, as well as some of the main output parameters. Moreover, we show how minor changes in the used training protocol can result in altered timecourses of behavioral outcomes that may represent independent subprocesses within the motor skill learning process.

Protocol

The experiments presented here were approved by the Veterinary Office of the Canton of Zurich, Switzerland and were carried out according to national and institutional regulations.

1. Feeding conditions
Note: All training sessions are performed under a scheduled feeding protocol.

1.1. Feed the rats 50 g/kg of standard chow once per day, after training is completed. This amount of food is sufficient to prevent major weight loss (body weight is >90% of free-feeding weight), but small enough to ensure reproducible behavioral conditioning. Weigh the rats daily to ensure their body weight remains stable.

Note: Additional overnight food deprivation may be useful prior to the first reward-touch session (step 2.3).

2. Training procedure for a reach-and-pull task
2.1. Preparation
2.1.1. Allow the rats to habituate to their new home cages for at least a week after arrival in the animal facility. Handle the rats regularly during this time and give dustless precision

pellets in the home cage to habituate the rats to the new food. These pellets will be used as rewards throughout the training protocol.

2.2. Habituation:

2.2.1. Place the rats in the testing cage for 30-45 min and provide 30-50 pellets in the feeding bowl, mixed with powdered chow. Open and close the cage window and run the pellet dispenser occasionally to habituate the rats to their sound. Repeat this for 2-3 days.

2.3. Reward-touch: Train the rats to touch the spherical handle through the cage window and to then move to the opposite side of the cage to retrieve a food reward.

2.3.1. Adjust the software settings so that the handle is located just outside the testing cage window at the start of each trial and align the handle with the center of the cage window. When the trials are successful, i.e., as soon as a light touch on the handle (0.25 mm displacement in any direction) has been detected, a tone sounds and a reward is dispensed. Trials are classified as failed when no touch has been detected for 180 s after the window opens.

2.3.2. Put the rat in the training cage. Prompt the rat to reach out by letting it grab at a pellet held near the handle. Direct the rat's attention to the handle and food bowl by tapping on the cage.

2.3.3. Stop prompting when the rat independently reaches through the cage window and retrieves the food pellet.

2.3.4. Continue until 100 trials (touches) are completed or until 60 min have passed, whichever comes first.

2.3.5. Continue training for 3-4 days and begin the next stage of training (step 2.4) when rats achieve 100 trials within 30 min on 2 consecutive days.

Note: Do not over-train this step. The goal of reward-touch is to achieve reliable interaction between the rat and robot, so that this behavior can be shaped in subsequent training.

2.4. Free pull (FP): Train the rats to reach out and pull the robot's handle.

2.4.1. Adjust the software settings so that the handle is located 18 mm from the window at the start of each trial, and must be pulled for at least 10 mm without interruption for a successful trial. There are no lateral restrictions on the pulling movement in this stage.

2.4.1.1. Classify a trial as failed when the handle has not been moved for 180 s after the window opens, when the handle is moved outside of the reachable workspace (more than 12 mm from midline), or when the rat has pulled less than 10 mm within 5 s after the first touch has been detected.

2.4.2. Take note of the number of times the left and right paw are used during the first 20 trials of the first FP session. The paw that is used in at least 80% of the trials is considered the preferred paw.

Note: Paw preference may already be clear in reward-touch sessions.

2.4.3. Move the handle laterally until it is aligned with the edge of the window to facilitate pulling with the preferred paw (i.e. move the robot 5 mm to the left side of the window for right-handed rats and vice-versa).

Note: Place the handle in this exact same position relative to the cage for all following training sessions for this rat. Exact placement is assured by marks on the cage wall and on the robot.

2.4.4. Put the rat in the training cage and train until 100 trials are completed or until 60 min have passed, whichever comes first.

Note: If the rat does not reach out far enough, prompt by letting it grab at a pellet held near the handle. Rats may stop trying to pull after repeated failed attempts. Tap on the cage, let them grab for pellets held with a pair of forceps or dispense a pellet to restore their motivation.

2.4.5. For experiments involving only FP training, continue training as described in 2.4.

Note: Typically, 1-2 FP sessions are needed to help transition from reward touch to SP training. The goal of these FP sessions is to habituate rats to reach out, grab and pull the handle, rather than to only touch it. As with reward-touch training, it is important not to over-train if the goal is to transition to a next training step.

2.5. Straight pull (SP): Train the rats to pull the handle without deviating more than 2 mm from midline.

Note: The midline is defined relative to the start position of the robot, not to the midpoint of the cage window. Thus, a pulling attempt ending at the midpoint of the cage window will result in a pulling trajectory that deviates more than 2 mm from midline.

2.5.1. Adjust the software settings so that only trials where the pulling movement does not deviate more than 2 mm from midline on either side are rewarded by a tone and a pellet. Keep all other parameters as described in step 2.4.

2.5.2. Put the rat in the training cage and train until 100 trials are completed or until 60 min have passed, whichever comes first.

Note: Rats may become extremely agitated and stop trying to pull after repeated failed attempts. Tap on the cage to redirect their attention to the reaching task, let them grab for pellets held with a pair of forceps or dispense a pellet to restore their motivation.

2.5.3. Continue training until rats reach plateau performance, or adapt the training period according to the goal of an experiment.

Representative results

Here, we show 3 variations of a reach-and pull task using male Long-Evans rats (10-12 weeks old). In the free-pull (FP) group (N=6), rats were trained to pull the robot's handle for a 22-day period without lateral restrictions. Animals in the straight-pull 1 (SP1) group (N=12) were trained to pull the handle without deviating more than 2 mm from midline. These animals transitioned directly from reward-touch (step 2.3) to straight-pull training (step 2.5). For both FP and SP1 animals, the handle was placed in the center of the cage window. These results were previously published in Lambercy et al.[10] Rats in the SP2 group (N=7) received 2 FP-training sessions before transitioning to straight-pull training. The handle was aligned with the edge of the cage window for this group, resulting is a slightly more difficult task, as the handle would deviate more than 2 mm from midline if pulled to the midpoint of the cage window.

All rats readily learn to interact with the robotic manipulandum (Figure 2A). The number of valid pulls (i.e. the number of pulling attempts where the handle is pulled at least 10 mm) increases rapidly and reaches stable plateau levels after 2-3 days in FP and SP1. The number of valid attempts increases at a comparable rate during the FP sessions of SP2, resulting in a stable number of valid pulls per session throughout SP training in SP2 rats. Plateau performance is high in all training paradigms and is independent of task parameters like handle position and limits on the permitted amount of deviation from midline.

SP1 rats reach plateau success rate (i.e. the percentage of valid pulls that remains within 2 mm of midline) after 5-4 training sessions (Figure 2B). SP2 rats show a slower progression and reach plateau success rate after 11 sessions, indicating that successful execution of this version of the straight pull task is more difficult to achieve. Final success rates are similar for SP1 and SP2.

During SP training, pulling trajectories become increasingly straighter, as evidenced by decreased deviation from midline (i.e. the area between the measured trajectory and midline) and resulting in an increased number of successful pulls in both SP1 and SP2 (Figure 3, Figure 5A). Interestingly, the average pulling trajectory of FP rats becomes straighter during the 22-day training period as well, although the amount of deviation from midline stabilizes at a higher level than in SP1 rats. This indicates that the natural pulling trajectory is relatively straight when the robot's handle is located in the center of the cage window. When the handle is aligned with the edge of the window, however, the puling trajectory is curved and deviation from midline remains stable during the SP2-FP sessions. Deviation from midline in the SP2 group remains higher than in the SP1 group, likely as a result of off-center handle placement.

Variability of the pulling trajectories (i.e. size of the 95% confidence interval) drops rapidly in FP and SP1, and reaches comparable levels in these groups after 3-4 training sessions (Figure 5B). Interestingly, SP2 animals do not show this decrease in variability and continuously pull with relatively low variability during SP sessions, but do show a rapid decline of trajectory variability during the SP2-FP sessions.

Similarly, both mean and peak pulling speed increase during initial training sessions (FP, SP1 and SP2-FP), but are stable during SP2 SP sessions (Figures 5C, D). Although average pulling speed does not change during SP2 sessions, pulling speed profiles become much less variable through training (Figure 4). This is reflected in both the number of submovements (i.e. number of accelerations and decelerations in the pulling movement, Figure 5E) and the number of trials with stops (i.e. trials where pulling velocity drops to zero, Figure 5F). After a strong decrease during the initial SP1 and SP2-FP sessions, both the number of submovements and the number of trials with stops continue to decrease in SP1 and SP2 throughout the 22-session training period. In FP rats, the number of submovements and trials with stops initially rapidly decrease as well, but stabilize at a higher level than both straight-pull groups and do not show a continued improvement. Interestingly, pulling speed does not seem to be closely related to the outcome of a trial (Figure 4).

The ≈5% of rats that do not successfully learn to perform the straight-pull task generally do learn to pull the handle, but are unable to pull straight (Figure 6). These animals show a consistently high deviation from midline, resulting in low success rates. Performance during SP2-FP sessions the animal presented here during is otherwise comparable to that of SP2 animals that do acquire the task successfully.

Figure 1: Overview of robotic manipulandum and handle positioning.
(A) Technical drawing showing the robotic manipulandum and marks for alignment with the training cage.
(B) Handle held in constant reference position at the start of a training session.
(C) Handle in free starting position at the start of a pulling trial.

Figure 2: Typical learning curves of a reach-and-pull task.
(A) Valid pulling attempts in a free pull task (FP, N=6), straight pull task without introductory FP-sessions (SP1, N=12) and a straight pull task (SP2, N=7) with introductory FP-sessions (SP2-FP). Values are mean ± s.e.m.
(B) Successful pulling attempts in the straight pulling task with (SP2) and without (SP1) introductory FP-sessions. Values are mean ± s.e.m.

Figure 3: Pulling trajectories become progressively straighter and less variable throughout training of the SP2 task.
Successful (black), failed (grey) and average (green) trajectories are shown for the first and final straight pull training session for a representative animal. Dotted lines show the 4 mm wide zone within which a successful trial is executed. The red dot denotes the starting position of the handle. The green dot shows the theoretical endpoint of a perfectly straight 10 mm pulling attempt.

Figure 4: Mean speed in the pulling direction of valid attempts increases slightly throughout training and becomes less variable from the first (A) to the last (B) training session.
Average (green) and individual pulling speed profiles of successful (black) and failed (grey) pulling attempts are shown for a representative animal carrying out the SP2 task.

Figure 5: An overview of parameters measured in a free pulling (FP, N=6) task, straight pull task without introductory FP-sessions (SP1, N=12) and a straight pull task (SP2, N=7) with introductory FP-sessions (SP2-FP). Values are mean ± s.e.m of all valid pulling attempts.
(A) Deviation from midline (area between the measured valid trajectories and a perfectly straight pulling attempt along midline, mm^2).
(B) Variability of pulling trajectories (95% confidence interval of all valid attempts within a session).
(C) Mean pulling speed of all valid attempts (mm/s).
(D) Peak pulling speed of all valid attempts (mm/s).
(E) Submovements as indicated by zero crossings in the acceleration profile of valid pulling attempts
(F) Pulling attempts with stops (% of valid pulls)

Figure 6: Example of an animal that does not successfully learn to perform the SP2 task. A) Pulling trajectories in the first and last training session. Successful (black), failed (grey) and average (green) trajectories are shown for the first and final straight pull training session for a representative animal. Dotted lines show the 4 mm wide zone within which a successful trial is executed. The red dot denotes the starting position of the handle. The green dot shows the theoretical endpoint of a perfectly straight 10 mm pulling attempt.
B) Learning curve showing valid and successful pulling attempts throughout the training period.

Discussion

Skilled reaching tasks are commonly used to study motor skill acquisition as well as impairment of motor function under pathological conditions[6]. Reliable and unambiguous analysis of reaching behavior is essential for the study of cellular mechanisms underlying motor skill acquisition, as well as neurophysiological processes involved in loss and subsequent recovery of function in animal models of neurological disease. The results presented here show how spatial and temporal aspects of the pulling movement show distinct profiles during motor skill training. These may reflect different subprocesses within the motor skill learning process[7,12].

In the results presented here, we show that even a small change in training protocol, such as a different starting position of the handle (SP1 vs. SP2), results in altered movement parameter profiles. By adding two FP sessions prior to straight pull training to our previously published training protocol[10], we were able to dissociate the effects of learning to pull from the skill to pull straight. In addition, the off-center placement of the robot's handle in this improved training protocol (SP2) results in a task with a shallower learning curve that is more advantageous for studying mechanisms of motor learning as it allows time for interventions before plateau performance levels are reached. Moreover, it is possible to distinguish factors related to task execution from factors related to task difficulty that are not immediately reflected in success rates, but may indicate further refinement of motor skill[4]. Smooth execution of the pulling movements, reflected in the number of submovements may be considered a measure of skilled, straight pulling. By contrast, spatial variability of the movement drops rapidly as the number of valid pulls increases in all three versions of the reach-and-pull task, but is not directly related to pulling success in straight pull tasks and may reflect general motor function or convergence on the correct movement required for a successful trial, rather than skilled task execution once the rules of the task have been learned.

Execution of our robotic reach-and-pull tasks is remarkably reliable and reproducible between animals. All trained animals acquire the free pull task, and a majority (90-95% of animals) is able to learn the straight pull task. Even animals that show consistently low success rates during straight pulling continue to execute a high number of valid pulling attempts. These failed, but valid attempts are fully recorded. Failed reaching attempts in a classical skilled reaching task typically results in an incomplete reaching movement. It is therefore not only possible to analyze aspects of the movement related to successful task acquisition, but also to assess which movement parameters result in failure.

While the measurements presented here give detailed information about pulling movements, not all aspects of the reach-and-pull forelimb movement are captured. Any changes in reaching behavior that occur prior to the first touch or after release of the handle at the end of a valid pulling attempt are not recorded and can therefore not be analyzed with equal precision. For example, the number of grabbing attempts prior to a pulling movement are not measured, even though they may be relevant in relation to functional recovery models. Analysis of high-speed video recordings provides this additional information. Previously described methods for movement tracking[13,14] can be adapted for this purpose.
Moreover, our recordings do not provide information about the quality of the rat's grip of the handle. Rotation of the handle, indicating pronation or supination of the paw, could provide some insight in combination with high-speed video. Since rotation and grip are particularly affected in rat stroke models [9,15,16], future experiments are needed to determine how effective the reach-and-pull tasks presented here are in capturing post-stroke motor deficits.

The tasks presented here were designed to mimic conventional single pellet reaching tasks: the required pulling distance is based on the typical distance between window and pellet in these tasks and the free movement of the handle within the horizontal plane enables measurement of the rat's natural paw trajectories over a 10mm distance in valid trials. Likewise, invalid trials where the handle is moved outside of the robot's workspace (e.g the handle is swiped aside during pulling) or where the pulled distance is insufficient could be interpreted as being similar to dropped pellets in single pellet reaching tasks, even though the handle does not drop to the floor when released.

This design captures more aspects of the pulling movement than automated tasks aimed at measuring a single simple movement. However, it also enables interaction between pulling and rotational movements and gives animals the opportunity for compensation. Insight into compensatory movements during motor function recovery may be valuable, but also complicates interpretation of the results.

A critical step in acquisition of the reach-and-pull tasks is successful conditioning of the reward touch step of training. Without reliable interaction between rat and robot, any further training steps are difficult to carry out and quantify reliably. It is equally important to not overtrain the rats during transitional training steps, however. While animals may continue to show improvements in performance during reward-touch training sessions for more than 3-4 days, over-consolidation prevents effective shaping of behavior in subsequent reach-and-pull training.

Constant placement of the handle is essential for correct execution and reliable analysis of any data obtained using the robotic reach-and-pull task presented here. While the position of the handle relative to rest of the robot and to midline is software-defined, the handle's position relative to the cage window is easily varied by moving either sideways. Here, we have shown how alignment of the handle with the either the edge or center of the window alters task acquisition and can be used to study processes underlying motor skill learning. Inconstant alignment of the handle within a training period, however, will introduce confounding effects and yields unreliable behavioral readouts.

In the protocol described here, rats are trained during daily sessions comprised of 100 trials, similar to our previous single pellet reaching experiments[4,17]. With automated training setups the number of trials per session can easily be increased, without requiring much more effort on the part of the researcher. While higher numbers of trials per session can result in lower intra-individual variability, the effects of increasing the number of trials per training session on the speed of learning and recovery has to be taken into account. Moreover, factors like satiety and fatigue will become more relevant and could interfere with performance in very long training sessions.

Although strain and sex differences in motor skill learning ability have been described in rats[4,18,19], we have obtained reliable performance in both male Sprague-Dawley and Long-Evans rats. Older animals (4-5 months old) are generally slower than younger ones (8-10 weeks) and show longer intervals between trials. Moreover, we have observed poor performance in older animals when food pellets are replaced with a sucrose-water reward. Older animals that receive liquid rewards experience difficulties when transitioning from reward-touch to pulling. This may be caused by age-related reward-preferences, or might indicate difficulties in understanding a more abstract reaching task in older animals (compared to conventional pellet reaching).

The robotic tasks can be varied in several ways: the required movement may be more or less precise (for example, a limited amount of deviation from a prescribed trajectory in a reach-and-pull task), or the robot may interfere with or assist the executed movement in any one or all of three dimensions (lengthwise or sideways movements in the horizontal plane and rotation angle of the handle). Other than variations on the reach-and-pull tasks presented in this paper, it is possible to design motor skill learning tasks where for example rotation angle of the handle, maximum movement velocity, or acceleration profile define the success of a trial.

Other than allowing easy variation of task parameters, the experimental setup presented here spatially separates the motor action from the given reward, which is dispensed on the opposite side of the cage. Adapting the reward size is not possible in classical reaching tasks without affecting task difficulty[20] (a smaller food pellet is more difficult to grasp than a larger one), nor is it possible to vary the chance of a reward independently of the animal's

skill level. Using a robotic task, the reward obtained for a motor action may be varied based on skill, current performance, or may be varied to assess factors such as motivation.
In conclusion, automated training combined with kinematic movement analysis provides an automated, objective method for studying motor skill learning that closely mimics conventional skilled reaching tasks, but yields additional data of both successful and failed pulling attempts. This approach opens up new avenues of investigation in combination with electrophysiological, pharmacological or optogenetic interventions aimed at enhancement of or interference with reach-and-pull movements or resulting food rewards.

Acknowledgements
This research was supported by the Swiss National Science Foundation, the Betty and David Koetser Foundation for Brain Research and the ETH Foundation.

Disclosures
The authors have nothing to disclose

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